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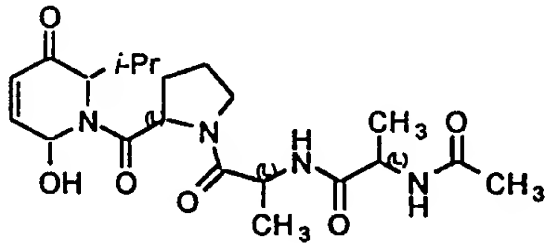
(54) Title: SERINE PROTEASE INHIBITORS

(57) Abstract

Compounds such as (A) or its pharmaceutically acceptable salts or hydrates, inhibit viral and human serine proteases, and are suitable for the treatment of hepatitis C virus infection, human cytomegalovirus infection, yellow fever, viral encephalitis, pulmonary emphysema, cardiovascular disease, cancer, rheumatoid arthritis, herpes, and immune nephritis.



(A)

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TITLE OF THE INVENTION
SERINE PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

Proteases are essential enzymes in the life cycle of many viruses and also play a role in various physiological processes. Many of the proteases developed by viruses are so specialized that they differ substantially from the enzymes to be found in the host, and such specialization makes the viral protease an attractive target of drug therapy. Proteases are also used by the body to regulate various processes and an imbalancing of these mechanisms leads to many disease states. Inhibition of protease, such as serine protease, is considered an ideal chemotherapy in such cases.

Viruses suitable for serine protease inactivation include hepatitis C virus (HCV), [Love, R. A., et al.; *Cell* 87, 331 (1996); Kim, J. L., et al., *Cell* 87, 343 (1996)], human cytomeglavirus (HCMV) [Stevens, J. T., et al, *Eur. J. BioChem.* 226, 361 (1994)], various flaviviruses, e.g., yellow fever, various encephalitises [Fraenkel-Conrat, H., et al., *Virology, 2nd Ed.*, Prentice Hall Englewood Cliffs, pp. 102-103 (1998)], as well as HSV-1, HSV-2, VZV, EBV, HHV-6, and HHV-7.

In the host, human leukocyte elastase (HLE) is a serine protease which is involved in diseases such as pulmonary emphysema, [Lungarella, G., et al., *Exp. Mol. Pathol.* 42, 44 (1985); Powers, J. C. *Trends BioChem. Sci.*, 1 (9), 211 (1976)], arthritis [Janoff, A. et al. (eds.) *Neutral Proteases in Human Polymorphonuclear Leukocytes*, Urban and Schwartzenberg, Baltimore, p. 390-417, (1978); Janoff, A. *Molecular Basis of Biological Degradative Processes*, Berlin, R.D., et al., (Eds.), Academic Press, New York, pp. 225-260, (1973)], pancreatitis [Geokas, M.C., et al., *Lab. Invest.* 19, 235 (1968)], adult respiratory distress syndrome [Burchardi, H., et al., *Adv. Exp. Med. Biol.* 167, 319 (1984)] and various degenerative skin disorders. The serine proteases involved with these diseases are of great interest as drug targets. Other physiological serine proteases include thrombin, which is implicated in many cardiovascular diseases [Fox, I., et al., *Thromb. Haemostasis* 69, 157(1993); Maffrand, J.P. *Nouv. Rev. Fr. Hemato.* 34, 405 (1992)]; urokinase-type plasminogen activator (UPA), which is known to aid in the metastasis of some types of cancer [Mueller, B. M., *Curr. Top. Microbiol. Immuno.* 213, 65 (1996); Schmitt, M., et al., *J. Obstet. Gynaecol.* 21, 151 (1995)], especially

prostate [Rabbani, S. A., et al., *Int. J. Cancer* 63, 840, (1995); Soff, G. A., et al., *J. Clin. Invest.* 96, 2593 (1995)], gastric [Herszenyi, L., et al., *Acta Physiol. Hung*, 83, 213 (1995); Plebani, M., et al., *Cancer* 76, 367 (1995)], and breast [Duffy, M. J., et al., *Enzyme Protein* 49, 85, (1996); Xing, R. H., et al., *Int. J. Cancer* 67, 423, (1996)]; and collagenase, which plays a role in destructive corneal disease associated with rheumatoid arthritis (Riley, G. P., et al., *Eye* 9(6), 703 (1995)]. Serine proteases are also implicated in immune nephritis [Hruby, Z., et al., *Int. Urol. Nephrol.* 20, 513 (1988); Hruby, Z., et al., *Nephrol. Dial. Transplant* 11, 32, (1996)].

Applicants have discovered new compounds useful for inhibition of serine protease as a drug target.

BRIEF DESCRIPTION OF THE INVENTION

Compounds of formulas I-III, as herein defined, are disclosed. These compounds are useful in the inhibition of the serine protease encoded by HCV, HCMV, flaviviruses involved with yellow fever or encephalitis, Herpes Simplex Virus, VZV, Epstein Barr Virus, and HHV. These compounds are also suitable for the treatment of infection by such viruses, the prevention of infection by such viruses, and in the treatment of diseases resulting from infection of such viruses. The compounds of the present invention are also useful for treating diseases without apparent viral etiology, including pulmonary emphysema, cardiovascular disease, cancer, rheumatoid arthritis and immune nephritis.

For such purposes, compounds of formulas I-III are suitable, either as compounds, pharmaceutically acceptable salts or hydrates, pharmaceutical composition ingredients, whether or not as combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating infection by such viruses, and methods of preventing infection by such viruses are also disclosed.

Some abbreviations that may appear in this application follow:

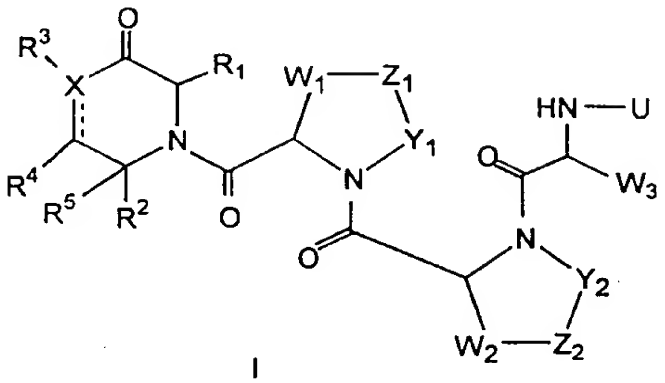
ABBREVIATIONS

EBV	Epstein Barr Virus
HCV	Hepatitis C Virus
HCMV	Human Cytomegalovirus
HHV	Human Herpes Virus
HLE	Human Leukocyte Elastase
HSV	Herpes Simplex Virus, in various serotypes, e.g., HSV-1, HSV-2
MCPBA	3-Chloroperoxybenzoic acid
UPA	Urokinase-type Plasminogen
VZV	Varicella Zoster Virus

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of formula I-III, combinations thereof, or pharmaceutically acceptable salts or hydrates thereof, in the inhibition of serine protease encoded by HCV, HCMV, HSV, VZV, EBV, HHV, and flaviviruses involved with yellow fever or encephalitis. The compounds of the present invention are also useful for treating diseases without apparent viral etiology, including pulmonary emphysema, cardiovascular disease, cancer, rheumatoid arthritis and immune nephritis.

Compounds of formula I are defined as follows:



I

wherein:

=---X is a single or a double bond;

X is C or N;

R^1 and R^4 are independently selected from the groups consisting of

(i) hydrogen;

(ii) C_{1-6} alkyl;

(iii) aryl;

(iv) C_{1-6}-OR, wherein R is H, C_{1-6} alkyl or aryl;

(v) C_{1-6}-SR; and

(vi) C_{1-6}-NR_2;

R^2 is

(i) OH;

(ii) C_{1-6} alkyl;

(iii) O-C_{1-6} alkyl;

(vi) aryl;

(v) C_{1-6}OR;

(vi) C_{1-6}-SR; or

(vii) C_{1-6}-NR_2;

R^5 is

(i) hydrogen;

(ii) C_{1-6} alkyl;

(iii) aryl;

when X is C or when X is N and

-----X is a single bond,

R^3 is H or $(CH_2)_n$-Q, wherein n is an integer between 1 and 5 and Q is

(i) OH;

(ii) NH_2;

(iii) NHR;

(iv) NR_2;

(v) COOH;

(vi) COOR;

(vii) SH;

(vii) S(O)R; or

(vii) SR;

when X is N and

-----X is a double bond,

R^3 is absent;

when either Y_1 or W_1 are hydrogen or Y_1 and W_1 are both hydrogens, then Z_1 is absent, Y_1 and W_1 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_1 and W_1 are both not hydrogen, they are selected independently from:

(i) $-CH_2-$;

(ii) $-CHR^1-$; or

(iii) $-CR^1R^4-$;

when either Y_2 or W_2 are hydrogen or Y_2 and W_2 are both hydrogens, then Z_2 is absent, Y_2 and W_2 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_2 and W_2 are both not hydrogen, they are selected independently from:

(i) $-CH_2-$;

(ii) $-CHR^1-$; or

(iii) $-CR^1R^4-$;

W_3 is selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

U is selected independently from:

(i) hydrogen;

(ii) $-C(O)-C_{1-6}$ alkyl;

(iii) -C(O)-aryl;

(iv) $-C(O)-O-C_{1-6}$ alkyl;

(v) -C(O)-O-aryl;

(vi) $-C(O)-NH-C_{1-6}$ alkyl; or

(vii) -C-(O)-NH-aryl;

Z_1 and Z_2 are selected independently from:

(i) $-CH_2-$;

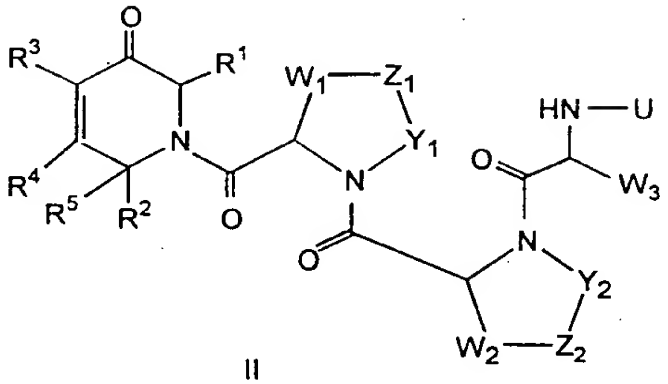
(ii) $-CHR^1-$;

(iii) $-CR^1R^4-$; or

(iv) $-CH_2CH_2-$;

or pharmaceutically acceptable salts or hydrates thereof.

Compounds of the formula II are defined as follows:



II

wherein:

R^1 and R^4 are independently selected from the groups consisting of

(i) hydrogen;

(ii) C_{1-6} alkyl;

(iii) aryl;

(iv) C_{1-6}-OR, wherein R is H, C_{1-6} alkyl or aryl;

(v) C_{1-6}-SR; and

(vi) C_{1-6}-NR_2;

R^2 is

(i) OH;

(ii) C_{1-6} alkyl;

(iii) O-C_{1-6} alkyl;

(iv) aryl;

(v) C_{1-6}-OR;

(vi) C_{1-6}-SR; or

(vii) C_{1-6}-NR_2;

R^3 is H or $(CH_2)_n$-Q, wherein n is an integer between 1 and 5 and Q is

(i) OH;

(ii) NH_2;

(iii) NHR;

(iv) NR_2;

(v) COOH;

(vi) COOR;

(vii) SH;

(viii) S(O)R; or

(ix) SR;

R^5 is

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when either Y_1 or W_1 are hydrogen or Y_1 and W_1 are both hydrogens, then Z_1 is absent, Y_1 and W_1 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_1 and W_1 are both not hydrogen, they are both $-CH_2-$;

when either Y_2 or W_2 are hydrogen or Y_2 and W_2 are both hydrogens, then Z_2 is absent, Y_2 and W_2 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_2 and W_2 are both not hydrogen, they are both $-CH_2-$;

W_3 is:

(i) hydrogen

(ii) C_{1-6} alkyl; or

(iii) aryl;

U is:

(i) hydrogen;

(ii) $-C(O)-C_{1-6}$ alkyl;

(iii) -C(O)-aryl;

(iv) -C(O)-O-C_{1-6} alkyl;

(v) -C(O)-O-aryl;

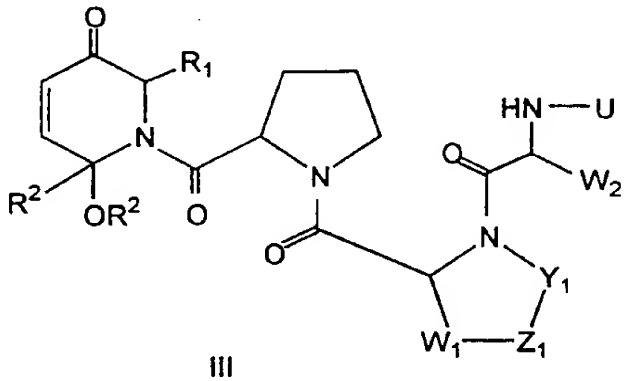
(vi) -C(O)-NH-C_{1-6} alkyl;

(vi) -C(O)-NH-aryl;

Z_1 and Z_2 are both -CH_2-;

or pharmaceutically acceptable salts or hydrates thereof.

Compounds of the formula III are defined as follows:



III

wherein:

R^1 is independently selected from the groups consisting of

(i) hydrogen

(ii) C_{1-6} alkyl;

(iii) aryl;

(iv) C_{1-6}-OR, wherein R is H, C_{1-6} alkyl or aryl;

(v) C_{1-6}-SR; and

(vi) C_{1-6}-NR_2;

R^2 is

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when either Y_1 or W_1 are hydrogen or Y_1 and W_1 are both hydrogens, then Z_1 is absent, Y_1 and W_1 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_1 and W_1 are both not hydrogen, they are both $-CH_2-$;

W_2 is:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

U is:

(i) hydrogen;

(ii) $-C(O)-C_{1-6}$ alkyl;

(iii) -C(O)-aryl;

(iv) $-C(O)-O-C_{1-6}$ alkyl;

(v) -C(O)-O-aryl;

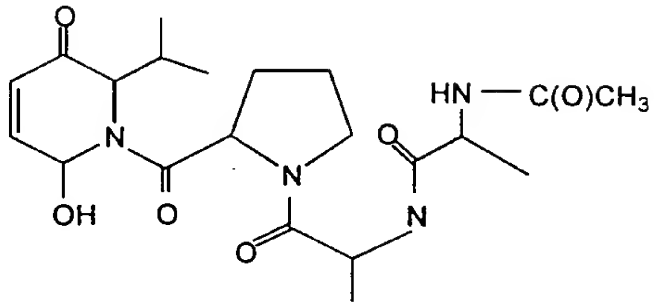
(vi) $-C(O)-NH-C_{1-6}$ alkyl; or

(vii) -C(O)-NH-aryl;

Z_1 is $-CH_2-$;

or pharmaceutically acceptable salts or hydrates thereof.

Compound A is preferred and is defined as follows:



IV

or pharmaceutically acceptable salts or hydrates thereof.

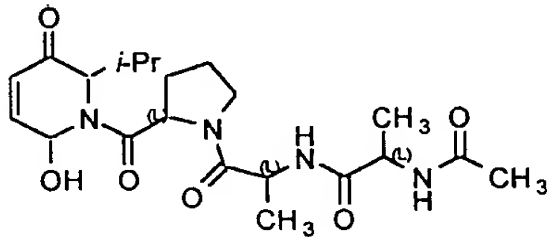
The present invention also relates to a pharmaceutical composition comprising any compound of the present invention, and a pharmaceutically acceptable carrier.

The pharmaceutical composition of the present invention is useful in the treatment of infections associated with hepatitis C and human cytomeglavirus, encephalitis, pulmonary emphysema, cardiovascular disease, cancer, rheumatoid arthritis and immune nephritis.

The pharmaceutical composition of the present invention is useful in the inhibition of the serine proteases of HCV, HCMV, HSV, VZV, EBV and HHV.

The preferred compound of the present infection is compound A, shown below

Compound A:



6-Hydroxy-2-isopropyl-1,6-dihydro-2H-pyridin-3-one, or pharmaceutically acceptable salt or hydrate thereof.

The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., R^1, R^2) occurs more than one time in any constituent or in formulas I-III, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

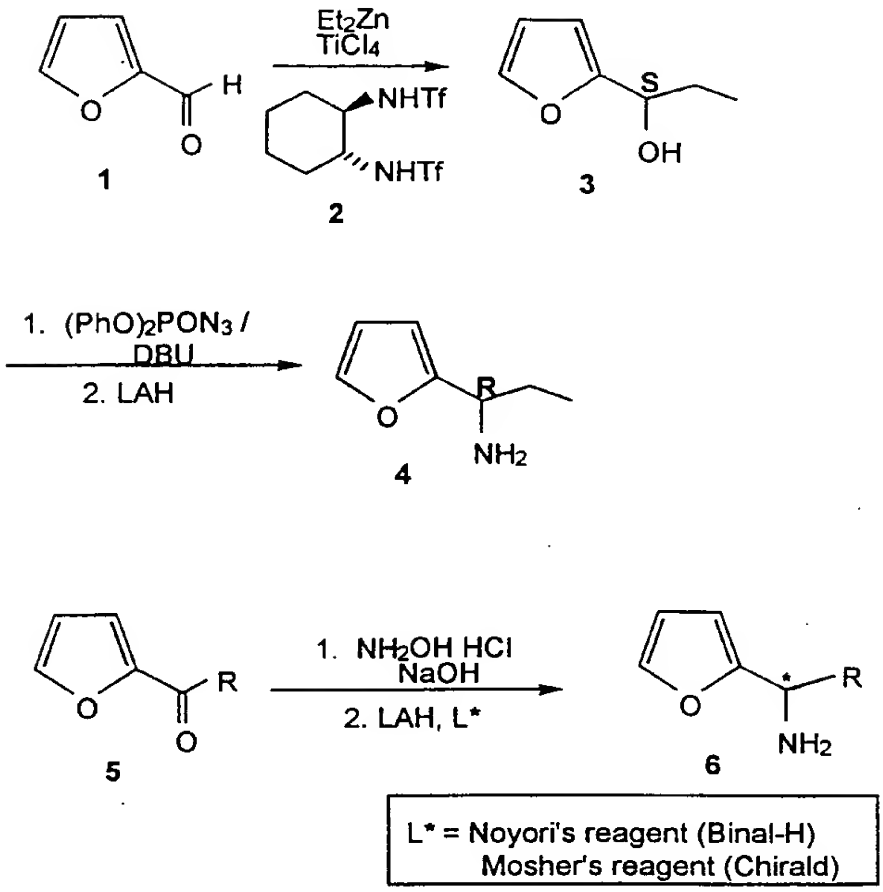
As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl). As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl.

The pharmaceutically-acceptable salts of the compounds of Formulas I-III (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methansulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Schemes I-V for preparing the novel compounds of this invention are presented below. Schemes I-V are not limited by any particular substituents employed in the schemes for illustrative purposes. The examples specifically illustrate the application of the following schemes to specific compounds.

To synthesize the end group **13** of the present invention, the corresponding alpha-furfuryl amide **11** is synthesized as an intermediate. In Scheme I, the asymmetric synthesis of the alpha furfuryl amide is carried out by first subjecting 2-furaldehyde **1** to enantioselective alkylation with a chiral sulfonamide-titanate complex, formed with **2**, to give **3** (in the S configuration) with typically high enantiomeric excess. See, e.g., Takahashi, H. et al., *Tetrahedron Lett.* 30, 7095 (1989), and Yoshioka, M. et al., *Tetrahedron Lett.* 30, 1657 (1989). Asymmetric conversion to the azide, followed by reduction to give amine **9** is accomplished by the method of Thompson, A. et al., *J.Org.Chem.* 58, 5886 (1993). Alternatively, acylated furan **5** is reacted with hydroxylamine to form the corresponding oxime, which in turn is reduced with lithium aluminum hydride (LAH) to give amine **6**, typically in the S configuration, in the presence of either Noyori's reagent or Mosher's reagent. See, e.g., Smith, H.E., et al., *J.Am.Chem.Soc.* 101, 5186 (1979); Hutchins, R.O. et al., *J.Org.Chem.*52, 704 (1987). Variations in Scheme I can provide either enantiomer. For example, inverting the configuration of both asymmetric carbons in **2** will give **3** in the **R** configuration.

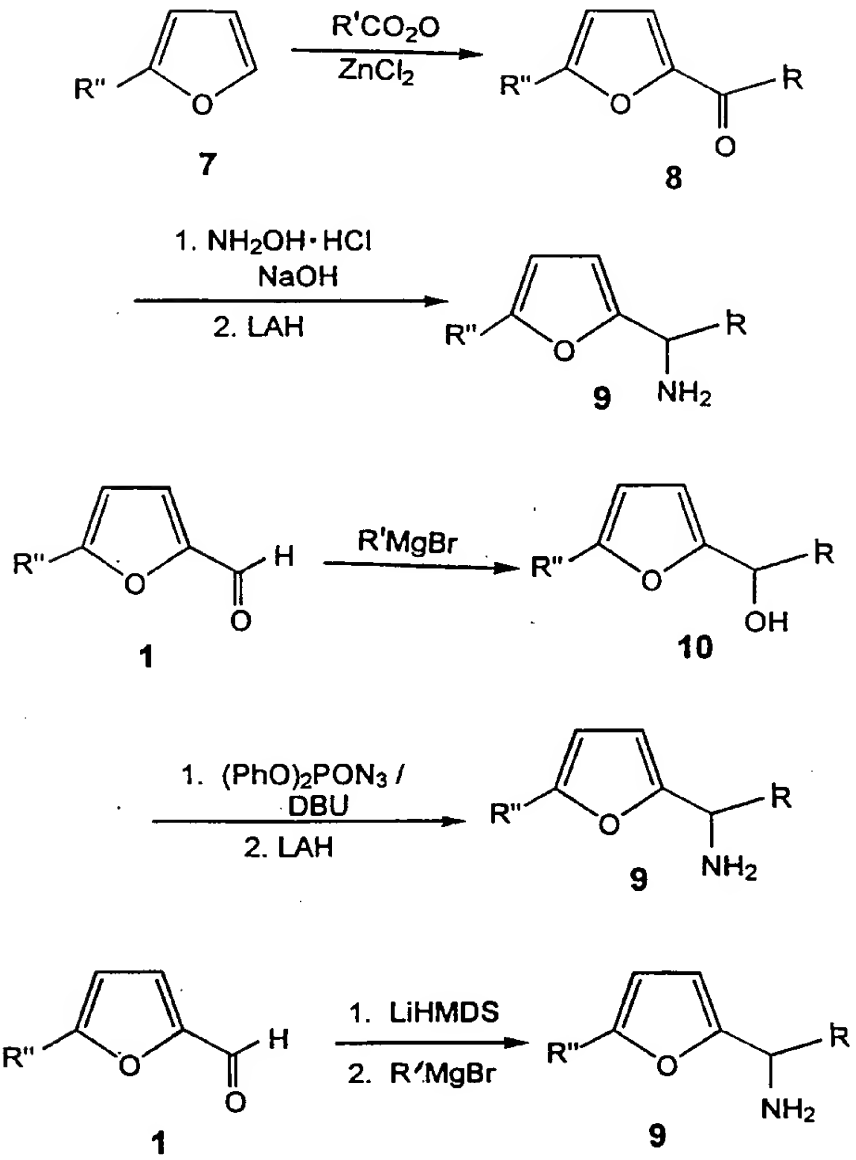
SCHEME I: Asymmetric Synth sis



Scheme II sets forth three racemic pathways for the synthesis of intermediate racemate **9**. In one pathway, furan **7** is acylated with catalyst $ZnCl_2$ according to Harough, H.D. et al., *J.Am.Chem.Soc.* 69, 1012 (1947). The acylated furan **8** is then reacted with hydroxylamine to form the corresponding oxime, which in turn is reduced with lithium aluminum hydride (LAH) to give the racemic amine **9**. See, e.g., Smith, H.E., et al., *J.Am.Chem.Soc.* 101, 5186 (1979). In a second pathway to synthesize racemic amine **9**, 2-furaldehyde **1** is first reacted with the appropriate Grignard reagent to give the racemic alcohol **10**. Conversion to the azide, followed by reduction to give racemic amine **9** is accomplished by the method of Thompson, A. et

al., *J.Org.Chem.* 58, 5886 (1993). A third method of synthesizing racemic amine **9** involves reacting the nonenolizable aldehyde **1** with 1,1,1,3,3,3-hexamethyldisilazane (LiHMDS) to give the corresponding N-trimethylsilyl imine, which is then treated with the appropriate Grignard reagent to give **9**. Tosylation of amine **9** gives **11** in Scheme III.

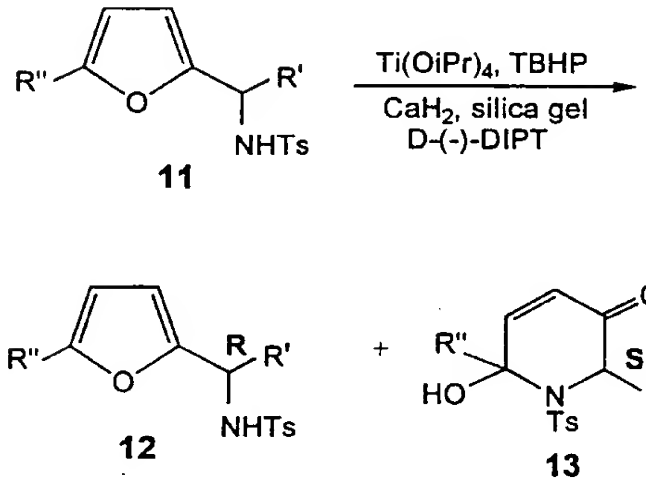
SCHEME II: Racemic Pathways



Oxidative rearrangements of **11** are carried out to isolate **13**. See, for example, Scheme III. In the methods of Zhou, W.-S. et al., *Tetrahedron* 49, 2641 (1993), Sharpless asymmetric epoxidation of racemic **11** using tert-butyl hyrdoperoxide (TBHP) in the presence of chiral titanium-tartrate catalyst gives a mixture of **12** and **13**.

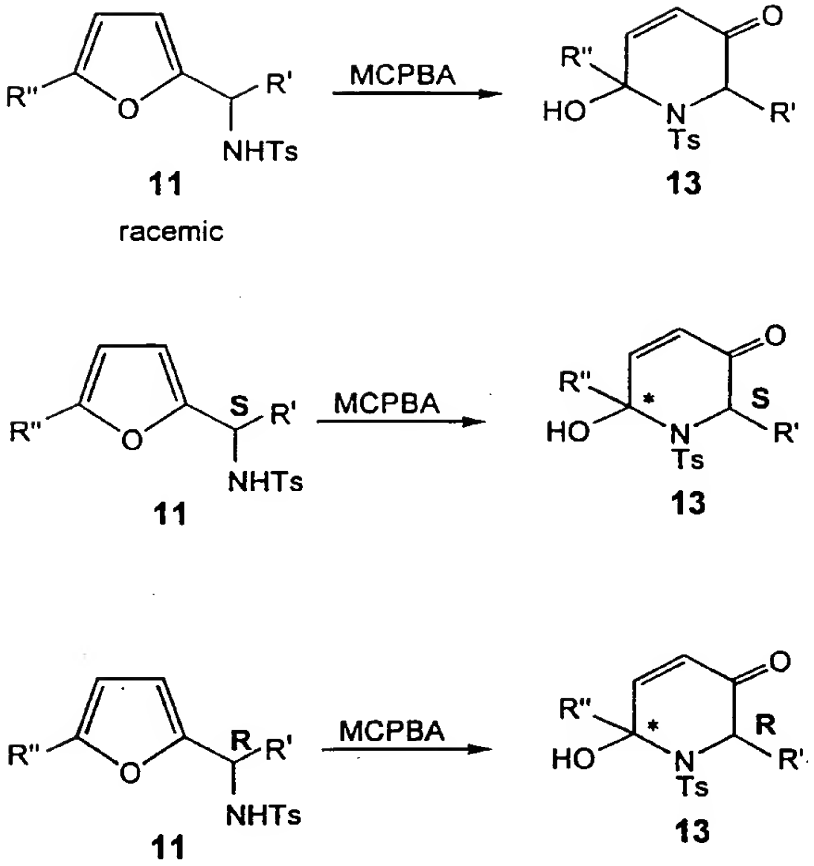
Alternatively, L-(+)-DIPT gives a mixture of **12** in the S configuration and **13** in the **R** configuration.

SCHEME III



In Scheme IV, oxidation of racemic **11** with MCPBA gives **13** as a mixture of two enantiomers. See, e.g., Zhou, W.-S. et al., *Tetrahedron* 49, 2641 (1993). Oxidative reaarangement of tosylate **11** with the S configuration provides **13** as one enantiomer, while starting material of the **R** configuration gives the other enantiomer.

SCHEME IV

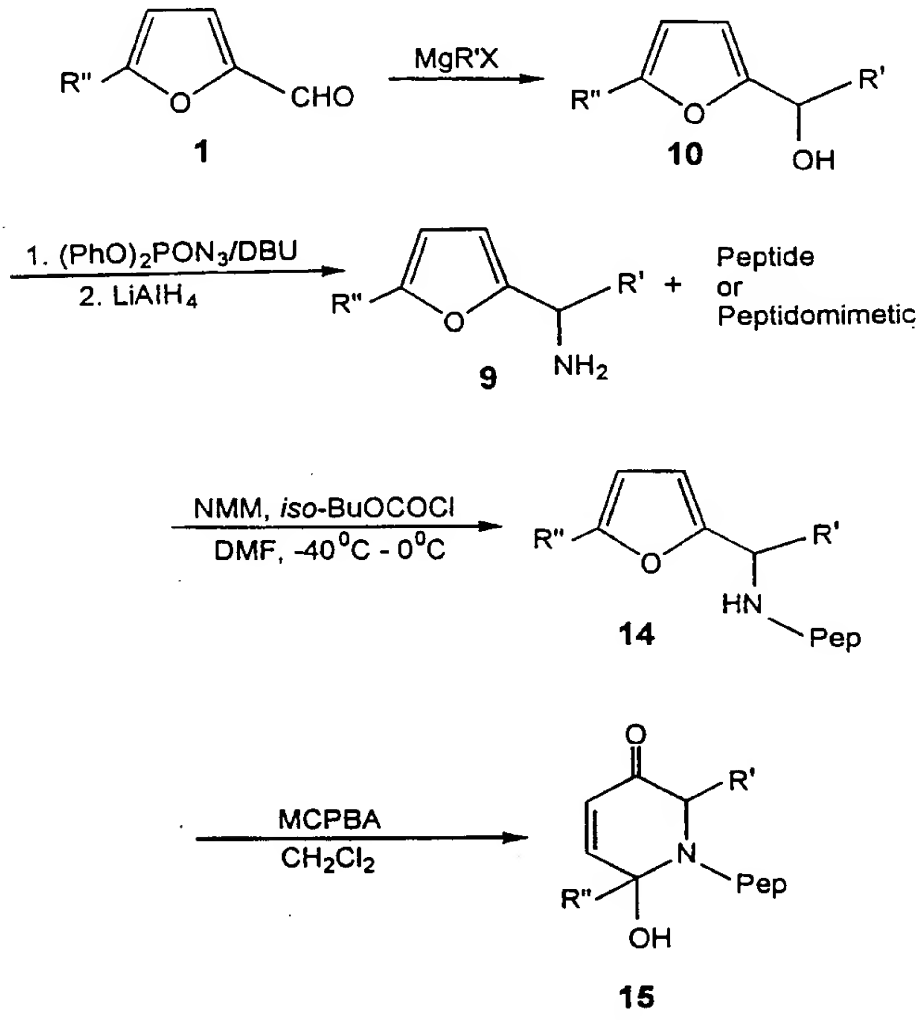


Amide couplings used to form the compounds of this invention are typically performed by the carbodiimide method with reagents such as dicyclohexylcarbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide. Other methods of forming the amide or peptide bond include, but are not limited to the synthetic routes via an acid chloride, azide, mixed anhydride or activated ester. Typically, solution phase amide coupling are performed, but solid-phase synthesis by classical Merrified techniques may be employed instead. The addition and removal of one or more protecting groups is also typical practice.

A general synthetic approach to compounds such as **A** is shown in Scheme V. Grignard addition to 2-furaldehyde **1** provides racemic alcohol **10**. Displacement with azide followed by LAH reduction gives racemic amine **9**. Coupling

of a peptide or peptidomimetic to amine **9** via the mixed anhydride provides racemic **14**, which is oxidatively rearranged using MCPBA to give compound 15 as a mixture of two enantiomers.

SCHEME V



The compounds of the present invention are useful in the inhibition of viral serine proteases, the prevention or treatment of infection by the human viruses encoding serine proteases, and the treatment of consequent pathological conditions such as Hepatitis C, yellow fever, viral encephalitis, herpes infection. The compounds of the present invention are also useful in the treatment of diseases without apparent viral

etiology, including, but not limited to pulmonary emphysema, cardiovascular disease, cancer, rheumatoid arthritis and immune nephritis.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, topically, intravitreously, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating infection by human viruses encoding serine proteases. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitble non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution,

or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

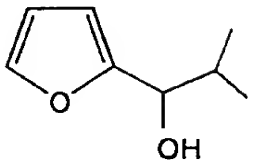
When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

Dosage levels of the order of 0.02 to 5.0 or 10.0 grams-per-day are useful in the treatment or prevention of the above-indicated conditions, with oral doses two-to-five times higher. For example, infection by Hepatitis C virus is effectively treated by the administration of from 10 to 50 milligrams of the compound per kilogram of body weight from one to three times per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the viral serine protease inhibitory compounds with one or more agents useful in the treatment of such viruses. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

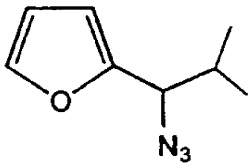
It will be understood that the scope of combinations of the compounds of this invention with antivirals, immunomodulators, anti-infectives or vaccines include in principle any combination with any pharmaceutical composition useful for the treatment of diseases resulting from infection by viruses encoding serine protease.

EXAMPLE 1



2-Isopropyl-2'-furyl carbinol. 2-Furaldehyde (18.25 g, 0.19 mol, 1.00 eq) was dissolved in THF (35 mL) and cooled to 0°C. To this solution, isopropyl magnesium chloride (99.71 mL, 0.21 mol, 2.0 M in THF, 1.05 eq) was added dropwise. After 2 h, TLC followed the consumption of the starting material, ice-cold NH_4Cl (5%; 50 mL) was added. The reaction solution was extracted with EtOAc (150 mL), washed with water (3 x 50 mL), dried ($MgSO_4$) and concentrated to a light yellow oil. Purification gave 2-isopropyl-2'-furyl carbinol (15.2 g, 0.11 mol, 57%). Chromatographic purification (Flash column, silica gel, 25 cm x 10 cm, 4/1; hexane/ethyl acetate); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27 (d, J=1.8 Hz, 1 H) 6.24 (dd, J_1=3.0 Hz, J_2=1.8 Hz, 1H) 6.13 (d, J=3.0 Hz, 1 H), 4.26 (d, J=6.9 Hz, 1H), 2.71 (s, 1 H), 2.00 (sept, J=6.6 Hz, 1 H), 0.92 (d, J=6.6 Hz, 3 H), 0.77 (d, J=6.6 Hz, 3H).

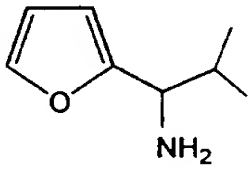
EXAMPLE 2



2-Isopropyl-2'-furylmethylazide. Following the procedure of Thompson, A.S., et al., *J. Org. Chem.* 58, 5886 (1993), 2-isopropyl-2'-furyl carbinol (12.50 g, 89.17 mmol, 1.00 eq) was dissolved in toluene (50 mL) and cooled to 0°C. To this

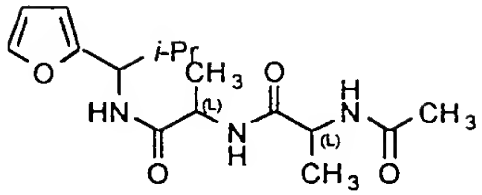
solution, DBU (16.0 mL, 107.01, 1.20 eq) was added followed by the addition of diphenyl phosphorus azide (12.93 mL, 107.01 mmol, 1.20 eq). The reaction mixture was stirred overnight and concentrated to a solid. The residue was passed through a pad of celite, washed with hexane and concentrated. Purification gave 2-isopropyl-2'-furylmethylazide (9.12 g. 55.21 mmol, 62%). Chromatographic purification (Flash column, silica gel, 25 cm x 10 cm, 19/1; hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 Mhz): δ 7.41 (d, J=1.2 Hz, 1 H), 6.37 (dd, J_1=3.0 Hz, J_2=1.8 Hz, 1 H), 6.30 (d, J=3.0 Hz, 1 H), 4.11 (d, J=7.2 Hz, 1 H), 2.19 (sept, J=6.6 Hz, 1 H), 1.04 (d, J=6.6 Hz, 3 H), 0.88 (d, J=6.6 Hz, 3H).

EXAMPLE 3



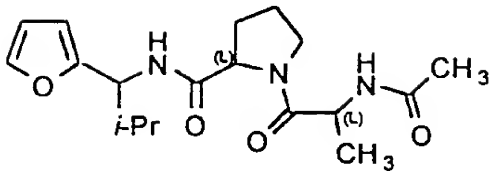
2-Isopropyl-2'-furylmethylamine. Following the procedure of Thompson, A.S., et al., *J. Org. Chem.* 58, 5886 (1993), 2-isopropyl-2-furylmethylazide (3.00 g, 18.16 mmol, 1.00 eq) was dissolved in THF (40 mL) and cooled to 0°C. To this solution, LAH (36.00 mL, 36.32 mmol, 2.00 eq) was added dropwise. After 2 h, the reaction was warmed to room temperature. The reaction was cooled to -78°C and quenched with water (50 mL). The reaction mixture was extracted with Et_2O (3 x 100 mL), washed with water (3 x 35 mL), dried ($MgSO_4$) and concentrated to give 2-isopropyl-2'-furylmethylamine (2.53 g, 18.16 mmol, 100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (d, J=1.8 Hz 1H), 6.30 (dd, J_1=3.0 Hz, J_2=1.8 Hz, 1 H), 6.11 (d, J=3.0 Hz, 1 H), 3.69 (d, J=6.2 Hz, 1 H), 2.04 (sept, J=6.6 Hz, 1 H), 1.04 (d, J=6.6 Hz, 3 H), 0.88 (d, J=6.6 Hz, 3H).

EXAMPLE 4



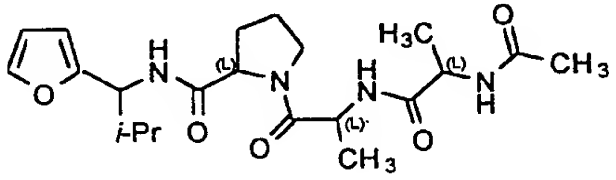
N-(L-Alanyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine. L-Alaninyl-L-alanine acetate (1.00 g, 4.95 mmol, 1.00 eq) was dissolved in DMF (15 mL) and THF (30 mL). The reaction mixture was cooled to - 20 °C (acetone/dry ice) and N-methyl morpholine (1.09 mL, 9.91 mmol, 2.00 eq) was added, followed by slow addition of iso-butyl chloroformate (0.70 mL, 5.40 mmol, 1.09 eq). The reaction mixture was stirred at - 20 °C (acetone/dry ice) for 1.5 hr, then cooled to -40 °C (acetone/dry ice), and 2-isopropyl-2'-furylmethylamine (0.83 g, 5.93 mmol, 1.20 eq) was added. The reaction was warmed to room temperature to stand overnight. The solvents were removed under reduced pressure. Purification gave N-(L-alanyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine as a white solid (1.45 g, 4.48 mmol, 91 %). Data: TLC (silica gel, 1:9; Methanol:EtOAc, R_f = 0.21); Chromatographic purification (silica gel, 2.5 cm x 10 cm, 100% hexane to 50% methanol in EtOAc); ^{1}H NMR (CD_3OD, 300 MHz): δ7.40-7.38 (m, 1 H), 6.33-6.30 (m, 1 H), 6.23-6.16 (m, 1 H), 4.76-4.71 (m, 1 H), 4.41-4.26 (m, 1 H), 2.20-2.13 (m, 1 H), 1.97-1.94 (m, 3), 1.36-1.29 (m, 6H), 0.96-0.82 (m, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ 175.3,175.1, 174.4,173.4,155.6,142.9,142.9, 111.2, 107.8, 107.7, 107.6, 54.8, 54.7, 54.6, 50.9, 50.7, 50.5, 50.4, 33.2, 33.1, 22.6, 20.0,19.4, 19.3, 19.2, 18.5,18.1, 18.0, 17.7, 17.5. Anal. Calcd for $C_{16}H_{25}N_3O_4$-0.5H_2O: C, 57.82; H, 7.58; N, 12.64; Found: C, 58.20; H, 7.82; N, 12.61

EXAMPLE 5



N-(L-Prolyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine. L-Prolyl-L-alanine Acetate (0.78 g, 3.42 mmol, 1.00 eq) was dissolved in DMF (35 mL). The reaction mixture was cooled to - 20 °C (acetone/dry ice), and N-methyl morpholine (0.75 mL, 6.84 mmol, 2.00 eq) was added followed by slow addition of iso-butyl chloroformate (0.44 mL, 3.42 mmol, 1.00 eq). The reaction was stirred at - 5 °C (acetone/dry ice) for 1.5 hr, then cooled to -40 °C (acetone/dry ice), and 2-isopropyl-2'-furylmethylamine (0.50 g, 3.42 mmol, 1.20 eq) was added. The reaction was warmed to room temperature to stand overnight. Work up and purification gave N-(L-prolyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine (0.82 g, 2.35 mmol, 69%). Data: TLC (silica gel, 1:1; Methanol:EtOAc, R_f = 0.40); Chromatographic purification (silica gel, 2.5 cm x 10 cm, 100% hexane to 33 % ethanol in EtOAc); ^{1}H NMR (CD3OD, 300 MHz): δ 7.40-7.38 (m, 1 H), 6.33- 6.30 (m, 1 H), 6.23-6.16 (m, 1 H), 4.76-4.71 (m, 1 H), 4.41-4.26 (m, 1 H), 2.20- 2.13 (m, 1 H), 1.97-1.94 (m, 3),1.36-1.29 (m, 6H), 0.96-0.82 (m, 6H).

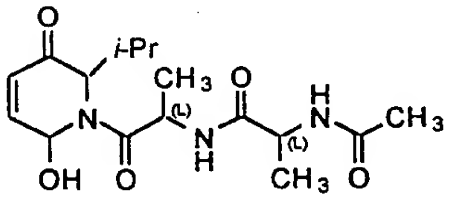
EXAMPLE 6



N-(L-Prolyl-L-alaninyl-L-alanine acetate)-2-isopropyl-2'-furyl methylamine. L-Prolyl - L-alaninyl-L-alanine acetate (0.72 g, 2.41 mmol, 1.00 eq) was dissolved in DMF (50 mL). The reaction mixture was cooled to - 20 °C (acetone/dry ice), and N-methyl morpholine (0.58 mL, 5.29 mmol, 2.20 eq) was added followed by slow addition of iso-

butyl chloroformate (0.31 mL, 2.41 mmol, 1.00 eq). The reaction was stirred at - 10 °C (acetone/dry ice) for 1.5 hr, then cooled to -40 °C (acetone/dry ice), and 2-isopropyl-2'-furylmethylamine (0.33 g, 2.41 mmol, 1.00 eq) was added. The reaction was warmed to room temperature to stand overnight. The solvents were removed under reduced pressure. Purification gave N-(L-prolyl-L-alaninyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine (0.83 g, 1.97 mmol, 81 %). Data: TLC (silica gel, EtOAc, R_f = 0.08); Chromatographic purification (silica gel, 2.5 cm x 10 cm, 50 % hexane in EtOAc to 33% methanol in EtOAc); ^{1}H NMR (CD_3OD, 300 MHz): δ 7.43-7.38 (m, 1 H), 6.34-6.16 (m, 2 H), 4.80-4.32 (m, 3H), 3.82-3.77(m, 1 H), 3.64-3.56 (m, 2H), 2.27-1.99 (m, 8H), 1.35-1.17 (m, 6H), 1.01-0.81(m, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ 174.7,173.8,173.8, 173.6, 173.4, 173.3, 173.3, 173.1, 172.9, 172.7, 155.9, 155.7, 155.5, 143.0, 142.9, 142.8, 111.2, 107.8, 107.7, 107.6, 107.5, 63.0, 62.4, 62.1, 61.8, 61.7, 61.6, 61.5, 61.4, 61.0, 60.6, 54.9, 54.8, 54.7, 54.6, 54.4, 50.5, 50.3, 48.4, 48.3, 48.0, 33.5, 33.4, 33.3, 33.1, 32.9, 32.11, 32.9, 30.8, 30.5, 30.2, 30.1, 26.1, 25.9, 25.7, 25.6, 23.6, 23.5, 22.8, 22.6, 22.6, 22.6, 20.1, 20.0,19.9, 19.6, 19.4, 19.3, 19.0. 18.6, 18.3, 18.2, 17.6, 17.2, 17.1. 17.0. 16.9. 14.6, 15.0.

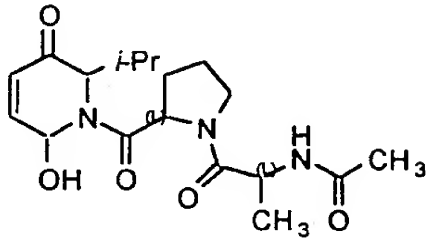
EXAMPLE 7



N-(L-alanyl-L-alanine acetate)-2-isopropyl-6-hydroxy-1,6-dihydro-3-piperidone. N-(L-alanyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine (18 mg, 0.06 mmol, 1.00 eq) was dissolved in dichloromethane (10 mL). To this solution, MCPBA (9.4 mg, 0.06 mmol, 1.00 eq) was added via four portions over 10 minutes intervals. After 10 hrs, the solvent was removed and the residue was passed through a pad of silica gel. EtOAc (50 mL) was used to washed away the impurities followed by washing with acetone (25 mL). The acetone solution was concentrated to give N-(L-alanyl-L-alanine acetate)-2-isopropyl-6-hydroxy-1,6-dihydro-3-piperidone as a white solid (1 5 mg, 0.04 mmol, 79%). ^{1}H NMR (CD_3COCD_3, 300 MHz): δ7.97-7.01 (m, 4H), 6.09-

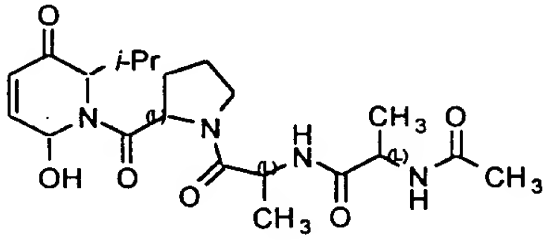
6.06 (m, 1 H), 4.35-4.00 (m, 3H), 1.93-1.83 (m, 3H), 1.31-1.14 (m, 3H), 0.95-0.82 (m, 3H). HRMS MH^+ (FAB) Calcd for $C_{16}H_{26}N_3O_5$: 340.1872. Found: 340.1871.

EXAMPLE 8



N-(L-Prolyl-L-alanine acetate)-2-isopropyl-6-hydroxy-1,6-dihydro-3-piperidone. N-(L-Prolyl-L-alanine acetate)-2-isopropyl-2'-furylmethylamine (35 mg, 0.10 mmol, 1.00 eq) was dissolved in dichloromethane (10 mL). To this solution, MCPBA (17 mg, 0.10 mmol, 1.00 eq) was added, After 1.2 hr, the solvent was removed and the residue was passed through a pad of silica gel. EtOAc (50 mL) was used to washed away the impurities followed by washing with acetone (25 mL). The acetone solution was concentrated to give a white solid, 25 mg. Chromatographic purification (silica gel, 0.5 cm x 1 cm, EtOAc to 33% acetone) gave N-(L-prolyl-L-alanine acetate)-2-isopropyl-6-hydroxy-1,6-dihydro-3-piperidone (10 mg, 0.03 mmol, 27%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33-6.03 (m, 4H), 4.72-4.46 (m, 2H), 4.13-4.01 (m, 2H), 3.82-3.45 (m, 3H), 2.37-1.81 (m, 8H), 1.31-1.26 (m, 3H), 0.99-0.80 (m, 6H).

EXAMPLE 9



N-(L-Prolyl-L-alaninyl-L-alanine acetate)-2-isopropyl-6-hydroxy-1,6-dihydro-3-piperidone. N-(L-Prolyl-L-alaninyl-L-alanine acetate)-2-isopropyl-2-furylmethylamine (46 mg, 0.11 mmol, 1.00 eq) was dissolved in dichloromethane (10 mL), To this solution, MCPBA (24 mg, 0.14 mmol, 1.25 eq) was added. After 1.5 hr, the solvent was removed and the residue was passed through a pad of silica gel. EtOAc (50 mL) was used to washed away the impurities followed by washing with acetone (25 mL). The acetone solution was concentrated to give a white solid, 35 mg. Chromatographic purification (silica gel, 0.5 cm x l cm, EtOAc to acetone) gave the title compound (15 mg, 0.03 mmol, 31 %) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96- 6.05 (m, 5H), 4.86-4.43 (m, 2H), 4.25-4.05 (m, 2H), 3.85-3.81 (m, 2H), 2.33-1.81 (8H), 1.39-1.27 (m, 6H), 1.00-0.80 (m, 6H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 173.3,172.9,172.4,172.2,172.1, 171.9, 171.8,171.6,171.0,170.7,170.1, 155.8, 154.4, 123.0, 122.5, 108.2, 69.8, 61.8, 61.5, 60.6, 60.0, 59.5, 58.5, 58.2, 58.1, 54.0, 49.0, 48.8, 47.4, 47.1, 47.0, 46.7, 46.4, 31.9, 29.9, 29.6, 29.4, 29.3, 29.1, 28.6, 25.4, 25.2, 25.1, 24.8, 24.6, 23.3, 22.7, 21.9, 19.9, 19.3, 19.0, 18.3, 18.1, 17.9, 17.5, 16.5, 14.3. HRMS MLi+ (FAB) Calcd for $C_{21}H_{32}N_4O_6Li$: 443.2482. Found: 443.2493.

EXAMPLE 10

Porcine Pancreatic Elastase Assay

The assay for inhibition of porcine pancreatic elastase was performed substantially according to Powers, J.C. et al. *Biochemistry* 29 3108. (1990). Porcine pancreatic elastase (PPE), Suc-Ala-Ala-Ala-NA (N-succinyl-alanyl-alanyl-alanine *p*-nitroanilide.), and Hepes were obtained from Sigma Chemical Co., St. Louis, MO. A volume of 50 µL of DMSO and a 50 µL aliquot of PPE solution (5.0 mg PPE dissolved in 5.0 mL 1 mmol HCl) were added to 0.5 mL Hepes buffer (0.1 M Hepes, 0.5 M NaCl, pH 7.5). A 50 µL aliquot of this solution was added to a solution of a 50 µL aliquot of substrate solution (20 mmol Suc-Ala-Ala-Ala-NA in DMSO) in 2.0 mL Hepes buffer. For tubes containing inhibitor, a 50 µL aliquot of inhibitor solution (20 mmole in DMSO) and a 50 µL aliquot of PPE solution were added to 0.5 mL Hepes buffer. Mixture was incubated for 10 minutes before a 50 µL aliquot was added to a

solution of a 50 µL aliquot of substrate solution in 2.0 mL Hepes buffer. 4-Nitroanilide hydrolysis was measured at 410 nm (ε = 8800 M^{-1} cm^{-1}) using a spectrophotometer. Slopes obtained for inhibitors were compared those of the corresponding V_0's.

Compound A was active in the assay, and showed about 20% inhibition at about 17 µM.

EXAMPLE 11

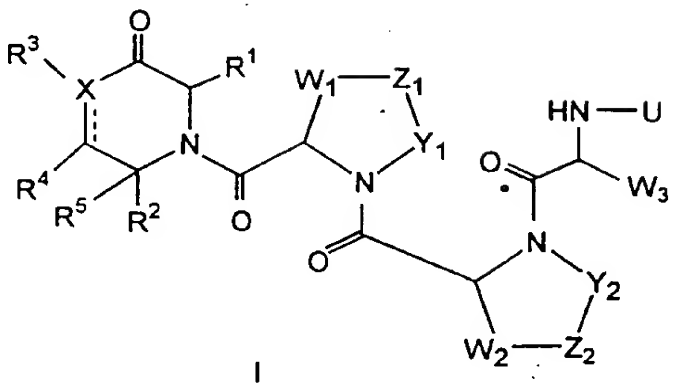
Human Cytomegalovirus Protease Assay

Inhibition of human cytomegalovirus protease is performed according to Pinko, C. et al., . *J.Biol.Chem* 270, 23634 (1995), using either the HPLC-based peptide assay or the continuous RET fluorogenic assay.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of the formula I



I

wherein:

-----X is a single or a double bond;

X is C or N;

R^1 and R^4 are independently selected from the groups consisting of

(i) hydrogen;

(ii) C_{1-6} alkyl;

(iii) aryl;

(iv) C_{1-6}-OR, wherein R is H, C_{1-6} alkyl or aryl;

(v) C_{1-6}-SR; and

(vi) C_{1-6}-NR_2;

R^2 is

(i) OH;

(ii) C_{1-6} alkyl;

(iii) O-C_{1-6} alkyl;

(vi) aryl;

(v) C_{1-6}OR;

(vi) C_{1-6}-SR; or

(vii) C_{1-6}-NR_2;

R^5 is

(i) hydrogen;

(ii) C_{1-6} alkyl;

(iii) aryl;

when X is C or when X is N and

-----X is a single bond,

R^3 is H or $(CH_2)_n$-Q, wherein n is an integer between 1 and 5 and Q is

(i) OH;

(ii) NH_2;

(iii) NHR;

(iv) NR_2;

(v) COOH;

(vi) COOR;

(vii) SH;

(vii) S(O)R; or

(vii) SR;

when X is N and

-----X is a double bond,

R^3 is absent;

when either Y_1 or W_1 are hydrogen or Y_1 and W_1 are both hydrogens, then Z_1 is absent, Y_1 and W_1 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_1 and W_1 are both not hydrogen, they are selected independently from:

(i) $-CH_2-$;

(ii) $-CHR^1-$; or

(iii) $-CR^1R^4-$;

when either Y_2 or W_2 are hydrogen or Y_2 and W_2 are both hydrogens, then Z_2 is absent, Y_2 and W_2 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_2 and W_2 are both not hydrogen, they are selected independently from:

(i) $-CH_2-$;

(ii) $-CHR^1-$; or

(iii) $-CR^1R^4-$;

W_3 is selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

U is selected independently from:

(i) hydrogen;

(ii) $-C(O)-C_{1-6}$ alkyl;

(iii) -C(O)-aryl;

(iv) $-C(O)-O-C_{1-6}$ alkyl;

(v) -C(O)-O-aryl;

(vi) $-C(O)-NH-C_{1-6}$ alkyl; or

(vii) -C-(O)-NH-aryl;

Z_1 and Z_2 are selected independently from:

(i) $-CH_2-$;

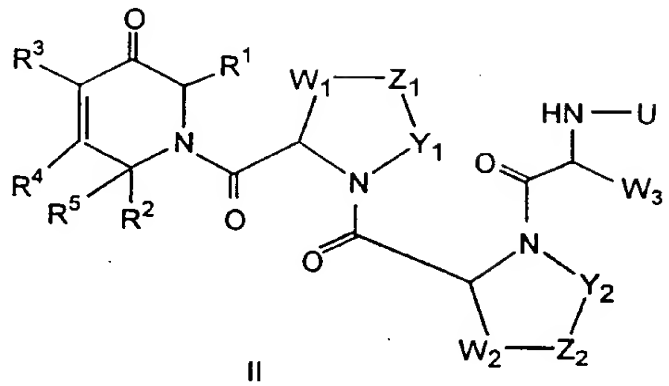
(ii) $-CHR^1-$;

(iii) $-CR^1R^4-$; or

(iv) $-CH_2CH_2-$;

or pharmaceutically acceptable salts or hydrates thereof.

2. A compound of the formula II



II

wherein:

R^1 and R^4 are independently selected from the groups consisting of

(i) hydrogen;

(ii) C_{1-6} alkyl;

(iii) aryl;

(iv) C_{1-6}-OR, wherein R is H, C_{1-6} alkyl or aryl;

(v) C_{1-6}-SR; and

(vi) C_{1-6}-NR_2;

R^2 is

(i) OH;

(ii) C_{1-6} alkyl;

(iii) O-C_{1-6} alkyl;

(iv) aryl;

(v) C_{1-6}-OR;

(vi) C_{1-6}-SR; or

(vii) C_{1-6}-NR_2;

R^3 is H or $(CH_2)_n$-Q, wherein n is an integer between 1 and 5 and Q is

(i) OH;

(ii) NH_2;

(iii) NHR;

(iv) NR_2;

(v) COOH;

(vi) COOR;

(vii) SH;

(viii) S(O)R; or

(ix) SR;

R^5 is

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when either Y_1 or W_1 are hydrogen or Y_1 and W_1 are both hydrogens, then Z_1 is absent, Y_1 and W_1 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_1 and W_1 are both not hydrogen, they are both $-CH_2-$;

when either Y_2 or W_2 are hydrogen or Y_2 and W_2 are both hydrogens, then Z_2 is absent, Y_2 and W_2 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_2 and W_2 are both not hydrogen, they are both $-CH_2-$;

W_3 is:

(i) hydrogen

(ii) C_{1-6} alkyl; or

(iii) aryl;

U is:

(i) hydrogen;

(ii) $-C(O)-C_{1-6}$ alkyl;

(iii) -C(O)-aryl;

(iv) -C(O)-O-C_{1-6} alkyl;

(v) -C(O)-O-aryl;

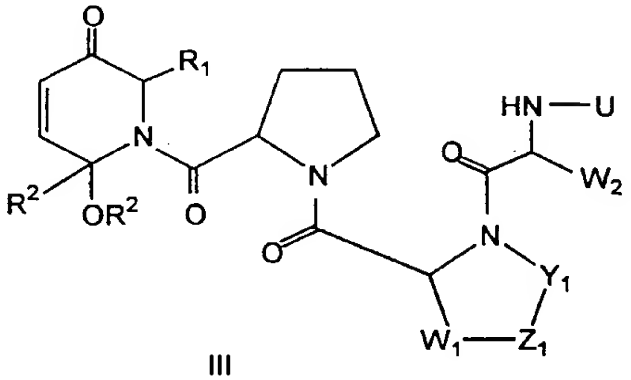
(vi) -C(O)-NH-C_{1-6} alkyl;

(vi) -C(O)-NH-aryl;

Z_1 and Z_2 are both -CH_2-;

or pharmaceutically acceptable salts or hydrates thereof.

3. A compound of the formula III



III

wherein:

R^1 is independently selected from the groups consisting of

(i) hydrogen

(ii) C_{1-6} alkyl;

(iii) aryl;

(iv) C_{1-6}-OR, wherein R is H, C_{1-6} alkyl or aryl;

(v) C_{1-6}-SR; and

(vi) C_{1-6}-NR_2;

R^2 is

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when either Y_1 or W_1 are hydrogen or Y_1 and W_1 are both hydrogens, then Z_1 is absent, Y_1 and W_1 are not joined to each other and are independently selected from:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

when Y_1 and W_1 are both not hydrogen, they are both $-CH_2-$;

W_2 is:

(i) hydrogen;

(ii) C_{1-6} alkyl; or

(iii) aryl;

U is:

(i) hydrogen;

(ii) $-C(O)-C_{1-6}$ alkyl;

(iii) -C(O)-aryl;

(iv) $-C(O)-O-C_{1-6}$ alkyl;

(v) -C(O)-O-aryl;

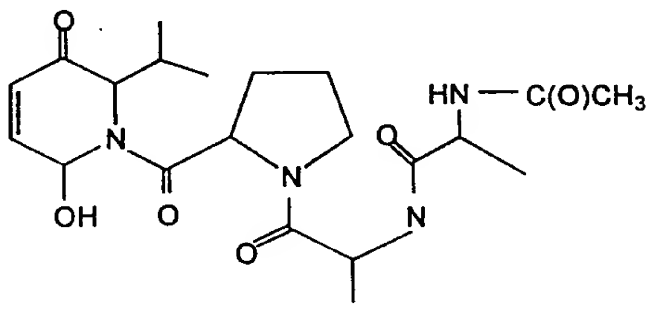
(vi) $-C(O)-NH-C_{1-6}$ alkyl; or

(vii) -C(O)-NH-aryl;

Z_1 is $-CH_2-$;

or pharmaceutically acceptable salts or hydrates thereof.

4. The compound IV



IV

or pharmaceutically acceptable salts or hydrates thereof.

5. A pharmaceutical composition comprising a compound of any of claims 1 - 4 and a pharmaceutically acceptable carrier.

6. The pharmaceutical composition of claim 5 useful in the treatment of infections associated with hepatitis C and human cytomeglavirus, encephalitis, pulmonary emphysema, cardiovascular disease, cancer, rheumatoid arthritis and immune nephritis.

7. The pharmaceutical composition of claim 5 useful in the inhibition of the serine proteases of HCV, HCMV, HSV, VZV, EBV and HHV.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07709

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 403/14, 403/02, 401/14, 401/02; A61K 31/495, 31/435, 31/55
US CL :544/359, 372, 361, 364; 546/188, 187, 189, 208; 540/597, 602

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/359, 372, 361, 364; 546/188, 187, 189, 208; 540/597, 602

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/07934 A2 (CHIRON CORPORATION) 23 March 1995, entire document.	1-7
A	EP 0 284 942 A2 (MERCK PATENT GESELLSCHAFT) 05 October 1988, entire document.	1-7
A	US 5,340,802 A (SHIOSAKI et al.) 23 August 1994, entire document.	1-7
A	US 5,190,922 A (LULY et al.) 02 March 1993, entire document.	1-7
A	US 4,534,897 A (MOON) 13 August 1985, entire document.	1-7
A	US 4,251,438 A (MOON) 17 February 1981, entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 JUNE 1998

Date of mailing of the international search report

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